

REMARKS

Claims 1-49 are pending. Reconsideration and allowance are respectfully requested.

The amendments to the claims find support throughout the disclosure as originally filed. In particular, claim 23 has been amended to clarify that the claimed invention is directed to a transgenic mouse with an active Flp transgene that causes sequence-specific recombination. Applicant submits that no new matter has been introduced by the above amendments.

A form PTO-948 has not yet been received. Applicant respectfully requests review of the formal drawings submitted in this application and return by the Official draftsperson of a form PTO-948 in the next Action.

35 U.S.C. 112

Claims 15, 41-42 and 47 were rejected under Section 112, 2nd paragraph, as allegedly indefinite. Applicant traverses.

The claims were amended to clarify the meanings of "developmental gene" and "essential gene" as suggested by the Examiner. Claims 15 and 47 were amended to clarify that an essential gene is a gene required for viability of a cell or organism. Similarly, claims 15, 41-42 and 47 were amended to clarify that a developmental gene is a gene controlling differentiation of a cell or development of an organism.

For the above reasons, Applicant requests withdrawal of the rejections under Section 112 because the claims are clear and definite.

35 U.S.C. 102

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131 quoting *Verdegaal Bros. v. Union Oil Co. Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The elements must be "arranged as in the claim." *Lindemann Maschinenfabrik v. Am. Hoist & Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984). In contrast, the references cited in the Office Action (Paper No. 14) do not disclose each and every element arranged as in the pending claims.

Claims 1, 2, 4-19, 22-27, 29-36, 41-43, 45 and 48 were rejected under Section 102(b) as being allegedly anticipated by Kilby et al. (1993). Applicant traverses.

On page 5 of the Action, the Examiner stated, "Kilby et al. suggests making exactly the transgenic animals instantly claimed" (emphasis added). This statement does not show that the public was put in possession of the claimed invention because although the art recognized the desirability of making Applicant's invention, there is an absence of evidence that the prior art established a reasonable expectation of success. At best, the Examiner's assertion about Wigley et al. provides

a motivation to make the claimed invention, but this is an insufficient basis for a rejection under Section 102. In the absence of a disclosure that teaches each and every element of the claimed invention (i.e., the claimed transgenic mouse, method, and system) arranged as in the claims, a *prima facie* case of anticipation has not been made.

Claims 1, 2, 4-13, 22-27, 29-33, 41-43, 45 and 48 were rejected under Section 102(b) as being allegedly anticipated by Wigley et al. (1994). Applicant traverses.

On page 5 of the Action, the Examiner stated, "Wigley et al. suggest making exactly the transgenic mice instantly claimed" (emphasis added). This statement does not show that the public was put in possession of the claimed invention because although the art recognized the desirability of making Applicant's invention, there is an absence of evidence that the prior art established a reasonable expectation of success. At best, the Examiner's assertion about Wigley et al. provides a motivation to make the claimed invention, but this is an insufficient basis for a rejection under Section 102. In the absence of a disclosure that teaches each and every element of the claimed invention (i.e., the claimed transgenic mouse, method, and system) arranged as in the claims, a *prima facie* case of anticipation has not been made.

Furthermore, the Examiner's attention is directed to the attached Declaration of Dr. Robert Hammer that states, to the best of his knowledge, Applicant was the first person to make the claimed invention. See ¶8 of the attached Declaration.

The references cited in the Action do not show that transgenic mice in accordance with the claims were made prior to the invention thereof by Applicant.

For the above reasons, Applicant respectfully requests withdrawal of the rejections under Section 102.

35 U.S.C. 103

Claims 1, 2, 4-13, 15, 22-27, 29-33, 37-43, 45 and 47-48 were rejected under Section 103(a) as allegedly unpatentable over Lakso et al., Wigley et al., Marx, Marshall, and Bieche et al. Applicant traverses.

Claims 3, 21, 28, 44, 46 and 49 were rejected under Section 103(a) as allegedly unpatentable over Wigley et al., Panigrahi et al., O'Gorman et al., Wahl et al., Hartley et al., and Buchholz et al. Applicant traverses.

Claims 1, 12, 15, 20, 24, 43 and 47 were rejected under Section 103(a) as allegedly unpatentable over Orban et al. and Wigley et al. Applicant traverses.

The comments below apply to the three claim rejections made under Section 103. In the interest of brevity, the arguments made in the Response of January 14, 1999 are incorporated herein. Although it is understood that the Examiner was not persuaded by those arguments, it is Applicant's intent to preserve them for appeal. Thus, the comments below are restricted to those points newly made by the Examiner.

The Examiner does not dispute that Lakso et al. fail to teach or suggest that Flp recombinase will be active in transgenic mice.

On page 6 of the Action, the Examiner states that the approach of Wigley et al. would necessarily result in transgenic mice expressing FLP recombinase" (emphasis added). Applicant disagrees that such expression would necessarily occur. No evidence of record shows there was a reasonable expectation of success that mere integration of a Flp recombinase construct into the genome would result in its expression. Moreover, the claimed invention requires that there be sufficient recombinase activity to catalyze recombination between Flp-recognition sequences. No evidence has been provided from which it could be concluded that there was a reasonable expectation that such a level of Flp recombinase activity could be successfully achieved in transgenic mice.

With respect to O'Gorman's assertion that Flp works nicely in transgenic mice, Applicant notes that the evidence is mixed. O'Gorman's assertion is not corroborated by any publication that Applicant is aware. When there is contradictory pieces of evidence, they must be weighed against each other to determine whether there was a reasonable expectation of success. Cf. M.P.E.P. § 2143.01 ("where the teachings of the prior art conflict, the Examiner must weight the suggestive power of each reference"). When the negative published reports of several groups working with ES cells is weighed against the uncorroborated report of a single investigator

(i.e., O'Gorman), it should be apparent the prior art did not show there was a reasonable expectation that a sufficient level of Flp recombinase activity could be achieved in transgenic mice.

It appears that the Examiner is relying on the newly cited Barinaga (1994) reference as evidence that there was a reasonable expectation of success. If this is correct, Applicant respectfully requests that the Examiner indicate so in the next Action and provide an explanation why this does not constitute a new ground of rejection.

Finally, on page 10 of the Action, there is an invitation to submit evidence of failed attempts of others to make Applicant's invention. The attached Declaration of Robert Hammer responds to this invitation and the Examiner is respectfully requested to consider the facts and opinions therein.

Dr. Hammer performed the experiments described in the Declaration while a postdoctoral associate in Ralph Brinster's laboratory. Drs. Hammer and Brinster are widely recognized as experts in the production of transgenic mice and their use.

The experiments most relevant to the claimed invention are described in the Declaration. A first transgenic mouse was made with tandemly integrated constructs, each containing a Flp-recognition sequence. This transgenic line was then used to produce fertilized eggs and they were injected with a Flp recombinase construct to make second transgenic mice. No recombination of Flp-recognition sequences was detected in the second transgenic mice.

In other experiments where it was attempted to provide Flp recombinase activity by injecting enzyme into fertilized eggs or transiently expressing an injected Flp gene in fertilized eggs, no recombination of Flp-recognition sequences was detected.

For the above reasons, Applicant respectfully requests withdrawal of the rejections under Section 103.

Having fully responded to the Office Action (Paper No. 14), Applicant submits that the pending claims are allowable and an early Notice to that effect is earnestly solicited. If further information is needed, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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